Council for Responsible Nutrition
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October 16, 2017

Ms. Michelle Ramirez
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, California 95814
Via Email: p65public.comments@oehha.ca.gov

Re: OEHHA Request for Comments on Possible Listing of n-Hexane

Dear Ms. Ramirez:

The Council for Responsible Nutrition (CRN) respectfully submits the following comments in response to the Office of Environmental Health Hazard Assessment's (OEHHA's) announcement regarding the availability of hazard identification materials for *n*-Hexane, and the possible listing of *n*-Hexane by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) at a public meeting scheduled for November 29, 2017. If the DARTIC determines that *n*-Hexane should be listed under Proposition 65, CRN requests that OEHHA adopt a No Significant Risk Level (NSRL) or safe harbor level that permits the presence of residual levels of *n*-Hexane in food products, including dietary supplements.

CRN, founded in 1973 and based in Washington, DC, is the leading trade association representing the manufacturers and marketers of dietary supplements, functional foods, and their nutritional ingredients. CRN companies produce a large portion of the dietary supplements marketed in California and throughout the United States, and are committed to marketing safe, beneficial products in compliance with Proposition 65.

n-Hexane is a solvent used to extract edible oils that may be found in dietary supplement products, among other uses. In the absence of a guidance specific to food products such as dietary supplements, some supplement companies rely on a guideline developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) that addresses the presence of residual solvents such as *n*-Hexane.[1] ICH classifies *n*-Hexane as a Class 2 Solvent that is not associated with severe toxicity, but should be limited to protect patients from potential adverse effects.[2] The ICH guideline recommends a

[1] ICH's mission is to achieve greater harmonisation worldwide for technical guidelines and requirements for pharmaceutical products while protecting public health. ICH guidelines are developed via a process of scientific consensus with global regulatory and industry experts working side-by-side. Additional information about ICH's Process of Harmonisation and procedures can be access here: http://www.ich.org/products/process-of-harmonisation/formalproc.html.

[2] ICH Harmonised Guideline, Impurities: Guideline for Residual Solvents, Q3c(R6), Current Step 4 version (October 20, 2016), available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C__R6___Step_4.pdf.

Permissible Daily Exposure (PDE) of 2.9 mg/day and a concentration limit of 290 ppm.[3] Acceptable exposure levels for Class 2 residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals, and use the method adopted by the International Program on Chemical Safety. This method is similar to the methods used by FDA in its Red Book guidance and by the Environmental Protection Agency's Integrated Risk Information System Process. The PDE is derived from the no observed effect level, or the lowest observed effect level and uses multiple factors to extrapolate from animal models to human exposure.[4]

Regulatory bodies including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada[5] follow the ICH guideline for residual solvents. In addition, US Pharmacopeia (USP), a standard-setting organization for the dietary supplement, food, and medicine industries, has adopted the same levels in its requirements for residuals solvents.[6] Although the ICH guideline is intended for drug products and USP standards are not required for dietary supplement products, some companies follow these guidelines on a voluntary basis.

CRN looks forward to working with OEHHA on the development of an appropriate safe harbor level for *n*-Hexane. The ICH guideline provides one example of a safe, science-based limit that OEHHA should consider if the DARTIC moves forward with listing *n*-Hexane. Without a safe harbor level for this substance, the dietary supplement and food industries will be forced to place unnecessary warnings on their products.

Thank you for the opportunity to provide these comments. Please do not hesitate to contact me should you have any questions or require additional information.

Sincerely,

Rend Al-Mondhiry
Associate General Counsel

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[3] *Id*. at 6.
[4] *Id. at* 15; Appendix 3. Methods for Establishing Exposure Limits.
[5] FDA, Q3C-Tables and List, Guidance for Industry, available at: https://www.fda.gov/downloads/drugs/guidances/ucm073395.pdf; EMA, Impurities Guideline for Residual Solvents, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/03/WC500104258.pdf; Health Canada, Guidelines for Residual Solvents, available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/impurities-guideline-residual-solvents.html.
[6] USP General Chapter <467>, available at: https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c467.pdf.